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Review Article

Multiple Myeloma and Occupational Risk Factors: A Narrative Review

Alireza Hejrati [1], ***Sadaf Parvin*** [2], ***Mehrnia Omidali*** [2], ***Lina Hejrati*** [3], ****Bahareh Shateri Amiri*** [4]

1. *Department of Internal Medicine, School of Medicine, Hazrat-e Rasool General Hospital, Iran University of Medical Sciences, Tehran, Iran*
2. *School of Medicine, Iran University of Medical Sciences, Tehran, Iran*
3. *School of Medicine, Hazrat-e Rasool General Hospital, Iran University of Medical Sciences, Tehran, Iran*
4. *Department of Internal Medicine, School of Medicine, Hazrat-e Rasool General Hospital, Iran University of Medical Sciences, Tehran, Iran*

***Corresponding Author:** Email: shateri.b@iums.ac.ir

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Abstract

Multiple Myeloma (MM) is a neoplastic hematologic disorder caused by the excessive proliferation of plasma cells and leads to bone lesions, anemia, and kidney failure. No definite etiology has been proposed for MM, but several environmental and genetic risk factors have been implicated so far. Exposure to pesticides, benzene, and organic solvents like methyl chloride have been considered a potential risk factor. Asbestos, ionizing radiation, and wood dust exposure have also been associated with MM. As MM is a relatively rare condition, the number of studies is insufficient, and in many studies, only a few study participants recall exposure to any agents. Therefore, establishing a definite risk factor is cumbersome and further studies with large study samples are needed. By recognizing these occupational risk factors, clinicians can encourage employees to reduce their exposure as more as possible and implement precautionary measures. In this review, we highlighted the current research on the potential association between occupational exposures and MM. Because of these studies, new regulations with the goal of occupational exposure reduction are anticipated in the future.

Keywords: Multiple myeloma; Plasma cells; Risk factors; Occupational exposure; Pesticides

Introduction

Multiple myeloma (MM) is a hematological malignancy associated with bone marrow plasma cells' malignant proliferation (1). It primarily affects males over 65 and represents about 0.8% of yearly new cancer cases worldwide (2). MM manifestations are fatigue, bone pain and lesions, hypercalcemia, renal insufficiency, anemia, and monoclonal antibodies in plasma and urine (3). Due to the rare nature of MM, limited research has been done to determine the etiology of this disease (4). However, advanced age, male gender, genetic predisposition, and hazardous occupational exposures are some of its risk factors (5, 6). Previous researches have addressed several potential occupational hazards for MM (1, 7, 8).

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Pesticides have long been speculated as carcinogenic agents (9). Surveys have addressed a higher risk of MM in pesticide-exposed workers (e.g., farmers) (10, 11). However, pesticides are not the only hazardous exposure in agriculture, and exposure to animals is associated with increased risk among farmers (12). Working with organic solvents in the painting, cleaning, and cosmetic industries has also been tied to a greater MM risk (5, 13, 14). Benzene is an organic solvent used in painting, plastic, and petroleum industries, and is a well-known cytotoxic agent (15). Some studies suggested a possible link between benzene and MM greater risk (16, 17). However, the results on the role of benzene are inconsistent and further research is required to explain this association (18). Other solvents such as xylene and toluene used in paints also have been linked to MM but the data is very limited and no definite conclusion cannot be derived (18).

As the mechanism of MM development is still largely unknown, investigating potential occupational risk factors might help to understand better its etiology. It is hoped that knowing these hazards lead to reducing their use and result in a safer workplace. We aimed to elucidate earlier research findings on the relationship between occupational risk factors and MM.

Pesticides

In the last decade, the effects of pesticides, herbicides, and insecticides on cancers like MM have gained considerable attention (8, 19). Chronic use of pesticides has been associated with some solid organ tumors (e.g., breast and prostate) and blood malignancies (e.g., leukemia and MM) (10). Chronic exposure to pesticides can act as genotoxins and generate reactive oxygen species, which may lead to clonal expansion of normal lymphocytes (20). Pesticides also can dysregulate the innate immune system, which causes chronic inflammation and growth factor release, which can cause tumor expansion (21).

Farmers have a higher MM risk, probably due to chronic use of pesticides (22-24). Lope et al. (25) corroborated a higher MM risk in male agricultural workers (25). They found that even occasional but intense use of pesticides might play a role in excess risk among them (25). Lerro et al. (26) found increased MM risk among pesticide applicators after 20 years of follow-up (26). Interestingly, this result did not apply to their spouses (26). Tual et al. (8) suggested that an elevated risk among pesticide-exposed farmers is associated with the duration of exposure with farmers with more than 20 years of exposure having the highest risk (8). However, a shorter period of persistent work with pesticides has been associated with MM (10). A case-control study showed that even ten years of work, as a farmer is associated with increased odds ratio of MM and mortality rate (10). Many other studies have corroborated this positive association between pesticides and MM (9, 11, 24, 27-32). Nandakumar et al. found no evidence of higher risk among people having farmer fathers, suggesting that only direct exposure is considered a risk factor for MM (33).

On the other hand, not all studies agree on the connection between pesticides and MM (34-36). Farmers are at higher risk but this risk is not related to pesticide exposure. It might be due to other factors, such as chronic exposure to zoonotic viruses (35). Among occupations exposed to pesticides, only nursery workers and gardeners had an elevated risk of MM and farmers were not at increased risk (37). This discrepancy might be due to the kind of pesticide and duration of usage (37). Little work has been done to investigate the role of each kind of pesticide on MM (38). Permethrin, a widely applied insecticide, has been categorized as possibly carcinogenic (39). Literature has also proposed a positive association between permethrin usage and MM (39). A study found an excess number of immature granulocyte (39). This alteration suggests abnormal hematopoiesis, especially in the myeloid lineage in the bone marrow following permethrin exposure (39). Glyphosate as another commonly used herbicide may be a culprit in developing MM, however, the data on this matter is limited (40). A positive connection between two other types of pesticides (phenoxyacetic acids and DDT) and MM has also been found (38). Farmers exposed

to carbamate pesticides, phenoxy herbicides, and organochlorines are at higher risk of MM (29, 41, 42). Scientists also evaluated the risk of MM among organochlorine pesticide applicator spouses and found some positive associations, in contrast with the previously mentioned findings (26). Understanding the harmful effects of pesticides and their association with MM might guide clinicians to warn farmers against their use and encourage them to reduce their exposure as much as possible (43).

Animal contact

Previous surveys have investigated the impact of other farming exposures like animal contact (28, 44). Farmers' exposure to zoonotic viruses, fungi, hair, dust, and animal saliva may act as an antigen affecting the immune system, resulting in abnormal clonal expansion (23).

Farmers working with sheep are exposed to the Orf virus (a member of the Pararpoxvirus genus in the Poxvirus family) which might alter their immune system and predispose them to MM (9). Parapoxvirus Orf virus contains an interleukin-10 gene homolog affecting myeloma cell proliferation (9). In contrast, this article found no excess risk among farmers exposed to beef, pig, and chicken (9). Some studies have also investigated chronic animal exposure in jobs other than farming (1, 45). For instance, veterinarians are at a higher risk of MM (45). In addition, fishermen have a higher mortality rate of multiple myeloma (1). It could result from higher fish consumption and, as a result, a higher concentration of organochlorine toxins (1). In contrast, in a Canadian study, eating fish more than twice a week can protect against multiple myeloma (46). This discrepancy is probably due to the different ecology and pollution of the different regions

Organic Solvents

Many occupations like painting and cleaning use chlorinated solvents on a daily basis (13, 14). A link between organic solvents and MM is reported (13, 14). This increased risk is mainly owed to chronic exposure to solvents like trichloroethane (TCE), chloroform, and methylene chloride (10, 12, 15, 47). The exact mechanism of carcinogenicity of organic solvents is not precisely known (48). Based on molecular studies on animals, solvents like TCE and chloroform can demethylate DNA, which can alternate tumorigenesis (i.e., expression of oncogenes or silencing tumor suppressor genes) (48).

TCE could cause a higher risk of MM, especially in the setting of cumulative exposure (13). Methylene chloride is another organic solvent used in paint removers, metal cleaners, and aerosol propellants (14). Liu et al. (14) observed an elevated risk of MM due to methylene chloride exposure (14). Chloroform or trichloromethane was historically used as an anesthetic. However nowadays, due to its carcinogenicity, it is used merely as a solvent. In the study of Gold et al. a slight rise in the risk of MM in chloroform-exposed workers has been suggested (13).

Other solvents, like aromatic hydrocarbon solvents, such as xylene and toluene, were linked to an elevated risk of MM (40). An important point to remember is that most of these studies are based on questionnaires and can be influenced by recall bias. Thus, extensive research with larger sample sizes is needed to corroborate these data.

Benzene

As an aromatic compound in natural gas and unrefined crude oil, Benzene is a probable occupational risk factor for MM (16). Upstream petroleum workers have the highest exposure to oil products containing benzene based on previous studies (16). Benzene affects bone marrow cells and consequently causes blood malignancies (20). The association between benzene and Acute myeloid leukemia and Chronic lymphocytic leukemia and have been noted in previous studies (20). An increased risk of multiple myeloma was also reported, especially for long-term usage (i.e., more than 15 years) (20). Acute myeloid leukemia risk decreases after exposure to Benzene, MM can be seen in more extended latency periods. In addition, the carcinogenic effect of chemical hazards depends on the metabolizing ability of the individuals (49). Glutathione-S-transferase theta (GSTTI) is an enzyme in the benzene detoxifica-

tion pathway in the liver. Lincz et al. (49) stated that individuals with a deficiency of GSTT1 are more susceptible to MM following benzene exposure (49). Nilsson et al. (50) suggested an increased MM risk among the deck crewmembers working on oil tankers, which might be due to benzene in oil products. This risk increases with the duration of exposure (50). In a mortality cohort study on chemical laboratory employees, a remarkably higher MM death among females was observed, probably due to benzene and radiation exposure (51). Based on the study, the MM death rate in male workers was slightly elevated, but this elevation was statistically non-significant (51). In a Swedish study, tanker workers who worked before 1985 had a higher risk of MM. Since then, modified ships have been introduced to reduce hazardous exposures like benzene (52). As expected, tanker workers hired after 1985 had no greater MM risk (52). However, not all the results are in favor of this association (53-55). A study on Australian petroleum workers failed to show any association between benzene and MM (15). Previously, a study on the mortality reports of petroleum workers was done. The workers required at least one year to be included in this study. No connection between exposure to petroleum products containing benzene and MM was discovered (17). Due to the discrepancy between the results, more investigations on the role of benzene in the development of MM is required in the future.

Asbestos

Asbestos, a mineral composed of long fibers, is commonly used in thermal insulation (56). It is a known carcinogen agent, particularly in mesothelioma and laryngeal malignancies (57). Several existing literature found no link between asbestos exposure and MM (18, 58, 59). Asbestos exposure and the incidence of MM are unrelated in Swedish construction workers (18). A case-control study nested in America also failed to prove any relationship between asbestos exposure and MM (59). On the contrary, some studies have shown an association between MM and asbestos (60-62). In a cohort study on Nordic firefighters, during a 45-year follow-up, the risk of MM was statistically higher among firefighters, mainly at the age of 70, possibly due to accidental exposure to released asbestos during building collapses (61). Seidler et al. found a higher risk of MM among subjects exposed to asbestos more than 2.6 fiber-year, indicating that the duration and intensity of exposure are related to the MM risk (62). To draw a definite conclusion, extensive studies on the asbestos role and MM is suggested in the future.

Coal

Research has found a connection between exposure to coal dust and the development of MM in Canadian men (63). Demers et al. (44) confirmed a higher MM risk in coal-exposed employees and that this risk increases with the length of exposure (23). La Vecchia et al. failed to prove any relationship between coal and MM (64). As a result, the association between coal and MM remains a topic of ongoing debate.

Electromagnetic field

For many years, scientists have explored the possible carcinogenicity of Electromagnetic fields (EMF) (38, 65). In the study of Milham et al., US radio operators were examined to see if there was a link between EMF and MM and results showed a significantly higher MM mortality rate (65).
Unfortunately, there is limited research regarding the connection between EMF and MM. Schroeder et al. looked into the risk of MM among workers exposed to EMF and failed to find any relationship between EMF and MM among electrical utility workers (66). Unexpectedly, a population-based case-control study found that EMF and MM might have a negative association, suggesting the protective effect of EMF on MM development (38).

Ionizing Radiation

The connection between uranium exposure in Gaseous Diffusion Plant employees and the development of MM was questioned. These workers are subjected to chronic low-level of uranium. They found a weak association between MM and

uranium exposure (67). Uranium miners are also exposed to radon regularly, which is a known carcinogen and has been linked to small-cell lung cancer (68). However, a study of Czech uranium miners showed no association between radon and MM (68).

Atomic bomb survivors from Hiroshima and Nagasaki who were exposed to high doses of radiation have experienced significantly higher rates of cancer (69). Thus, scientists analyzed the life span study cohort of survivors to determine the potential relationship between high radiation doses and MM, but no evidence was found of their association (70). However, an older study showed that survivors had a higher rate of MM, which increased with exposure intensity (69).

Wood

A handful of studies have evaluated the potential association between wood exposure and MM (5, 33, 44, 63). Working as carpenters might lead to a higher risk of MM, which is associated with the duration of exposure, especially more than 30 years (63). Having a carpenter parent might increase MM risk, which emphasizes the role of indirect exposure in MM development (33).Nevertheless, Demers et al. found a higher risk of MM in forestry and logging employees but showed no increased risk among carpenters (23).

Due to a possible association between wood and MM, using protective equipment such as masks or shields in wood-related industries is suggested. However, more research with large study samples is needed to assess the role of wood exposure in the pathogenesis of MM.

Other occupations

School teachers

MM risk was remarkably higher in schoolteachers probably due to vast exposure to the public and increased risk of infections with viruses, which may cause pathologic lymphatic proliferation (12). According to a case-control study in the US Among female teachers, those who worked in post-secondary school had the utmost risk (45). However, among male teachers, working in elementary schools had a higher chance of MM. Unfortunately, the exact cause of this matter remains poorly understood.

Housekeepers

Housekeepers typically have an elevated risk of developing cancer because of their exposure to various chemical compounds (10). A Danish study stated women considered as housekeepers based on their tax records, had a significantly elevated risk of MM (5, 10). Despite chronic exposure to cleaning compounds and various allergens, Perrotta et al. showed only a moderately increased MM risk in female cleaners (37).

Cosmetologists

Previous literature has argued a positive association between working as a cosmetologist and greater MM risk (12, 45).

Still, the number of studies is very limited and no definitive conclusion can be made (45). Gold et al. demonstrated an additional risk of MM among hairdressers (12). Barbers exposed to EMF from electric tools had a slightly elevated risk of developing MM (45). However, no greater risk was seen among Danish women who worked as hairdressers in a different study (5). These mixed results might stem from the fact that cancers such as MM, are strongly related to lifestyle factors (71). In addition, the contrast in results might imply that in each country, hairdressers use different materials and products, which have a unique impact on their health.

Painters

The risk of MM among painters has gained attention in the literature (6, 23). Paul et al. demonstrated an excess risk among painters primarily due to exposure to solvents, pigments, and additives (23). McLaughlin et al. showed a non-significant extra risk of MM among painters who work as varnish makers (6). However, the findings are contradictory and a pooled analysis research indicated no elevated risk of MM among painters (37). Painters might use different chemicals around the world, which might justify this heterogeneity in results (6). Therefore, more studies on the carcinogenicity of popular kinds of

paints and solvents used in each country are suggested.

Conclusion

Several risk factors have been implicated in the course of MM. The majority of the literature has worked on the role of pesticides, organic solvents, and benzene and many of them had suggested a potential association. Due to the limited number of studies, the effects of many other occupational exposures like asbestos, coal, electromagnetic field, and ionizing radiation on MM are unclear. The outcomes of many researches are contradictory because of the variations in the materials used by each industry in different parts of the world. Therefore, scientists should focus on the common chemicals used in each industry in their own country. By this method, better and more efficient health policies can be made in each region. It also enables the implementation of safety measures and leads to a safer work environment.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors have no conflict of interest

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